



A Pilot study evaluating whether treatment of scabies with ivermectin also treats headlice Ivermectin

IVM-LICE

ISRCTN
NCT (clinicaltrials.gov)

V1.0
16th May 2017

SPONSOR: London School of Hygiene & Tropical Medicine

FUNDERS: [Wellcome Trust](#)

STUDY COORDINATION CENTRE: LSHTM

LSHTM ethics reference: Pending

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Clinical queries should be directed to **Michael Marks** who will direct the query to the appropriate person.

Sponsor

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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This study is funded as part of a Wellcome Trust Research Fellowship held by Michael Marks.

This protocol describes the **IVM-LICE** study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

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GLOSSARY OF ABBREVIATIONS

AAH	Atoifi Adventist Hospital
AE	Adverse Event
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Event

KEYWORDS

Scabies
Ivermectin
Impetigo
Headlice

STUDY SUMMARY

TITLE A Pilot study evaluating whether treatment of scabies with ivermectin also treats headlice Ivermectin

DESIGN Prospective before and after pilot study

AIMS Assess the impact of a scabies treatment programme on the prevalence of headlice in the same community.

OUTCOME MEASURES Primary Outcome
a) Change in prevalence of headlice between baseline and follow-up

POPULATION Treatment is provided to all eligible residents for scabies. A total population of approximately 150 individuals will be treated

ELIGIBILITY All residents of the Atoifi Hospital Campus are eligible to participate in the study

TREATMENT *Treatment of scabies:*
Standard treatment in line with guidelines:
Either an oral dose of Ivermectin (200µg/kg) or permethrin cream and malathion shampoo for those with a contraindication to Ivermectin (WT<15kg, pregnant or breastfeeding women) given in 2 doses 7-14 days apart.

DURATION 3 months

1. INTRODUCTION

1.1 BACKGROUND

Scabies and headlice are both common worldwide ectoparasitic infections and scabies in particular is a significant public health problem in the Pacific[1]. Ivermectin is an effective treatment for both conditions. Community mass treatment is now the recognised best approach to treating scabies and household treatment is also commonly used for headlice treatment[2,3]. As ivermectin is used to treat both conditions it would be anticipated that programmatic scabies treatment in a community would also treat head lice. The aim of this small scale pilot study is to evaluate this hypothesis.

1.2 RATIONALE FOR CURRENT STUDY

Ivermectin is known to have a broad range of parasitic activities and is effective at treating many ectoparasitic infections. It is now considered the optimum drug for community treatment of scabies. The drug is also known to be effective for treating headlice but no studies have formally assessed whether community treatment for scabies also reduces headlice prevalence. This study will help us more fully understand any additional benefit on headlice when communities are treated for scabies

2. STUDY OBJECTIVES

Study Aims:

Assess the impact of a scabies treatment programme on the prevalence of head lice in the same community.

Primary Objective:

The primary objective is to see whether community treatment for scabies also reduces the prevalence of head lice.

3. STUDY DESIGN

This is a pilot open-label study measuring the impact of scabies treatment on head lice prevalence in the same individuals. In line with recommendations the treatment is provided at the community level.

Study Site

This study will be conducted on the campus of Atoifi Adventist Hospital. All staff and their families living on the campus will be invited to participate. Based on input from collaborators at Atoifi campus it is recognised that headlice is a common problem particularly amongst children living on the hospital campus. Treatment will be provided at the level of the community in line with recommendations and best evidence for scabies. All individuals on the campus will be offered treatment and will be invited to participate in the study.

Treatment will be provided at the level of the community in line with recommendations and best evidence for scabies. All individuals will be invited to participate in the study and will be offered treatment.

Community Awareness

Prior to the study commencing we will engage community leaders on at the hospital campus. A research training workshop will be held at AAH and which will be attended by AAH and other study staff as well as key community leaders. This meeting will provide an opportunity for explanation of the study aims and methodologies and for study staff to answer questions about the study design and implementation.

Eligibility Criteria:

All residents of the Atoifi Hospital campus will be invited to participate in the study.

Inclusion Criteria:

All residents of the selected communities will be invited to participate in the study.

Exclusion Criteria:

Individuals with a contra-indication to treatment.

Individuals not consenting to participate.

Duration

The duration of the study is 3 months. For all participants, there will be a 15 day on-study period which will include two visits by the study team

- Day 1 for baseline medical assessment and delivery treatment
- Day 8-15 for delivery of second dose of treatment

Treatment

No investigational medications or indications are being assessed. All individuals will receive standard treatment for scabies.

Treatment of scabies:

- Day 1 for baseline medical assessment and delivery of ivermectin (or permethrin & malathion when contra-indicated)
- Day 8 for delivery of second dose of ivermectin

An oral dose of Ivermectin (200µg/kg).

In individuals with a contra-indication (pregnancy, breast-feeding, weight <15kg) permethrin cream and malathion shampoo will be offered instead.

3.1 STUDY OUTCOME MEASURES

Primary Outcome

a) Change in prevalence of headlice between baseline and follow-up

Sample Size

The required sample size was calculated to be 150 individuals based on the following assumptions.

- Pre-treatment prevalence of headlice of about 25%
- Post-treatment prevalence of headlice of about 10%
- Enrolment 80%

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

3.2 RISKS AND BENEFITS

The safety profile of ivermectin is very well known. Safety has been well studied through its usage therapeutically and in large scale MDA programs. In the past 21 years, more than 1 billion doses of ivermectin tablets have been distributed for both onchocerciasis and lymphatic filariasis. Several studies of pregnant women accidentally given ivermectin showed no evidence of teratogenicity[4–6].

Participants will benefit from receiving treatment for scabies and headlice as part of the study. These are both major public health problems in the Solomon Islands and participants will therefore gain benefit from receiving the best available treatment for these conditions which, it is believed, will result in improvements in their health and well being.

Benefits to Communities

Communities will benefit from receiving treatment for scabies as part of these studies. This is a major public health problems in the Solomon Islands and participants will therefore gain benefit from receiving the best available treatment for this condition which, it is believed, will result in improvements in their health and well being.

Blinding

This is an open-label study

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 PRE-TREATMENT EVALUATIONS

Treatment of the whole community with Ivermectin and Permethrin is the best available treatment for the purpose of scabies control. Individual treatment results in re-infestation and treatment failure. In line with recommendation therefore treatments is offered to all individuals regardless of the presence/absence of clinical features of either disease.

4.2 INCLUSION CRITERIA

All consenting individuals in the participating communities will be eligible to participate

4.3 EXCLUSION CRITERIA.

Individuals not consenting to participate in the study.

Individuals who are unwell on the day that study medications are administered.

4.4 WITHDRAWAL CRITERIA

Study participation is voluntary and study participants can withdraw at any time. The number of withdrawals will be recorded and only data collected prior to withdrawal will be included in the analysis. Only data collected prior to withdrawal will be included in the analysis.

5. TRIAL MEDICATION

5.1 Name and description of investigational medicinal product(s)

No investigational treatments are being tried. Ivermectin (and permethrin) is a recognised treatment for scabies and is on the Solomon Islands Essential Drug List for this indication.

Ivermectin

Ivermectin is an anthelmintic. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. After oral administration, the apparent plasma half-life of ivermectin is approximately 16 hours. Ivermectin is indicated for the treatment of onchocerciasis or river blindness caused by *Onchocerca volvulus* and for strongyloidiasis caused by *Strongyloides stercoralis*. The recommended dosage for treatment of scabies is two oral doses designed to provide approximately 200µg of ivermectin per kg of body weight. The same dose is recommended in the Solomon Islands. Ivermectin is available in 3mg tablets.

Topical 5% permethrin cream (Lyclear®)

Topical 5% permethrin (Lyclear ®) cream for scabies is supplied in a 30g tube. The cream is applied all over the body including from neck to toe and washed off after a minimum of 8 hrs. For children aged 2 months or less permethrin should be washed off after 4 hours.

5.2 Legal status of drug

Permethrin is licenced in the UK for the treatment of scabies. It is listed as on the essential medicines list for the Solomon Islands and recommended as a potential treatment for scabies.

Ivermectin is not licenced for the treatment of scabies in the UK although NICE has provided guidance on its use (<https://www.nice.org.uk/advice/esuom29/resources/ivermectin-for-difficulttotreat-scabies-17546902981>). Ivermectin is widely used in control programmes for both Onchocerciasis and Lymphatic Filariasis. Ivermectin is listed as on the essential medicines list for the Solomon Islands and recommended as a potential treatment for scabies.

5.4 Drug Storage and Supply

Medications will arrive by plane and will reach the islands by boat at the provincial pharmacy / medical store. The order request will be checked with the supplies delivered. The delivery notice number, delivery date and the medications batch number will be recorded in a log book. Medications

will be taken out of the pharmacy in bulk by the study teams for dispensing in the community. Study teams will maintain a log of all medicines dispensed that can be cross-checked against participants study records.

WEIGHT	IVERMECTIN TABLETS (3mg Tabs)
<15KG	PERMETHRIN CREAM
15KG	1
25 – 37.5 KG	2
37.5 – 50 KG	3

5.5 Preparation and labelling of IMP

For participants receiving ivermectin, the dose will be determined according to body weight and treatment will be administered under direct supervision of the study team. Drug administration will be recorded in a standardized record form.

Participants assigned to permethrin (due to contra-indication to ivermectin) will receive a tube of cream and will be asked apply the cream from neck to toes before they leave the clinic and under supervision of a study nurse, and leave it on for a minimum of 8 hours, maximum 24 hours if possible. For children aged 2 months or less, cream will applied for a maximum of 4 hours.

5.6 Dosage schedules/modifications

In line with standard treatment the dosing of Ivermectin will use the following weight bands

Permethrin will be used instead of Ivermectin in the following circumstances

- Pregnancy
- Breastfeeding
- Child <6 months age
- Child <15kg

Where permethrin is indicated the following standard dosing protocol will be used:

- Full tube for adults.
- Half tube for children.
- Apply to whole body and leave on for 1 day before washing off

5.7 Known drug reactions and interaction with other therapies

50-75 KG	4
>75 KG	5

The safety profile of ivermectin is well established from large mass treatment

campaigns where >100 million doses have been administered. The most commonly reported side effects are for Ivermectin are headache, dizziness, itch. Adverse events are normally mild and self-limiting with no specific therapy required. Permethrin does not commonly cause any systemic adverse commons.

5.8 Concomitant medication

Individuals receiving Warfarin may not receive treatment with Ivermectin due to potential interactions. No individuals outside of the capital of the Solomon Islands (Honiara) are receiving Warfarin due to a lack of INR monitoring facilities and therefore it is not anticipated that any individuals in the study will be receiving a contra-indicated concomitant medication. Permethrin will be offered if a patient taking warfarin was identified.

5.9 Trial restrictions

There are no trial restrictions.

As noted above pregnant and breast feeding women and children <15kg will be offered permethrin rather than ivermectin but will still be allowed to participate in the study.

5.10 Assessment of compliance

Drugs will be delivered as a single observed treatment and therefore compliance will be assessed at the time of drug distribution.

6. SAFETY REPORTING FOR DRUG TRIALS

6.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	<p>Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.</p> <p>An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.</p>
Adverse Reaction (AR)	<p>Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>The phrase “response to an investigational medicinal product” means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none">• Results in death• Is life-threatening• Requires inpatient hospitalisation or prolongation of existing hospitalisation• Results in persistent or significant disability/incapacity• Consists of a congenital anomaly or birth defect <p>Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.</p>
Serious Adverse Reaction (SAR)	<p>An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.</p>
Suspected Unexpected Serious Adverse Reaction (SUSAR)	<p>A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:</p> <ul style="list-style-type: none">• In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product• In the case of any other investigational medicinal product, in the investigator brochure (IB) relating to the trial in question.

6.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related side effects due to the drugs used in this study. The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be reported.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

6.3 REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance.

6.3.1 Non serious Adverse Reactions (ARs)/Adverse Events (AEs)

Given the established safety profile of the drugs being used in this study and the fact that they are being used for established indications we will only collect data on SAEs and SUSARs.

6.3.2 Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information. The CI (for a single-centre trial) or PI (for a multi-centre trial) must record the event with an assessment of seriousness, causality and expectedness.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

6.3.3 SUSARs

All SAEs assigned by the PI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Regulatory Authority, in the UK: Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor (or delegate) will inform the MHRA, and the ethics committee of UK-relevant SUSARs within the required expedited reporting timescales (as per LSHTM Standard Operating Procedure for recording, managing and reporting of adverse events for IMP studies).

For blinded trials, all SUSARs must be reported assuming the active compound is involved.

In the case of a suspected, unexpected, serious adverse reactions (SUSAR), the staff at the site should:

1. Contact the study coordination centre immediately by phone or email to inform them of the event.
2. Submit a completed SAE form (signed and dated) within 24 hours, together with relevant treatment forms and anonymised copies of all relevant investigations.
3. Submit any additional information promptly upon request.

Contact details for reporting SAEs and SUSARs
Telephone: +677 7738438 / +44 7984 643424
Email: michael.marks@lshtm.ac.uk

7. ASSESSMENT AND FOLLOW-UP

Data Collection

At baseline all individuals will undergo a standardized examination to collect data on the presence of scabies, impetigo and headlice. Following examination individuals will be weighed and directly observed treatment will be dispensed in line with standard treatment guidelines (see below). Individuals will be re-examined at 48 hours to assess immediate killing of head-lice, again at 2 weeks and 3 months.

No samples are collected as part of this study

7.1 LOSS TO FOLLOW-UP

This is not an individually randomised clinical trial but allowance has been made for loss to follow-up in the sample size calculation.

7.2 TRIAL COMPLETION

The trial is planned to run over a 3 month period. The trial will be complete at the end of this 3 month period.

8. STATISTICS AND DATA ANALYSIS

Sample Size

The required sample size was calculated to be 150 individuals based on the following assumptions.

- Pre-treatment prevalence of headache of about 25%
- Post-treatment prevalence of headache of about 10%
- Enrolment 80%

Primary Outcome

a) Change in prevalence of headache between baseline and follow-up

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

9. MONITORING

9.1 RISK ASSESSMENT

This is considered a low risk study.

All the drugs being used are being prescribed for routine indications and have well established safety profiles. As such only passive monitoring for adverse events will be undertaken during the study.

9.2 MONITORING AT STUDY COORDINATION CENTRE

Data will be entered directly into an electronic database at the time of the study. Consent forms will be reviewed to ensure completion in line with GCP standards.

9.3 MONITORING AT LOCAL SITE

Site visits will take place at D1 (treatment scabies), D8 (second treatment for scabies) and month 3 (assessment of outcome). A random selection of consent forms and data collection forms will be reviewed at the baseline visits and adverse event and data collection forms at each subsequent visit.

10. REGULATORY ISSUES

10.1 ETHICS APPROVAL

The Study Coordination Centre has applied for ethics approval from the LSHTM Research Ethics Committee, as well as the Solomon Islands National Ethics Board and the [Atoifi Adventist Hospital Ethics Committee](#).

Substantial protocol amendments will not be implemented until a favourable opinion has been granted from both the ethics committee. Correspondence from both ethics committees will be maintained in the trial master file. As the duration of the study is 3 months the annual progress report will accompany the notification of the end of the study.

10.2 CONSENT AND CONFIDENTIALITY

Prior to performing any study specific procedure, written informed consent will be obtained for each subject. Information sheets explaining the study will be distributed to community nurses who will be trained in explaining the study. For subjects below the legal age, a parent or legal guardian must provide consent. Written consent will be obtained in local dialect on all occasions.

10.3 Confidentiality

All data will be fully-anonymised. A copy of the database will be held both at Atoifi Hospital and LSHTM. The study database will not contain any patient identifiable information. Forms will be retained at Atoifi Adventist Hospital.

10.4 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

10.5 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

10.6 FUNDING

This study is funded as part of a Wellcome Trust Research Fellowship held by Michael Marks. No payments will be made to patients participating in this study.

10.7 AUDITS AND INSPECTIONS

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

11. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Michael Marks and Jason Diau.

All treatments in the study are being given for standard indications and the drugs have known safety profiles including in the setting of co-administration. A DSMB will therefore not be appointed.

All data will be held jointly by LSHTM and AAH. Data will be stored on an encrypted password protected server at both LSHTM and AAH.

12. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

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